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Time to positivity as prognostic tool in patients with *Pseudomonas aeruginosa* bloodstream infection

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Summary *Objectives:* The time to positivity (TTP), measured as the time span between the start of incubation and the alert signal from the blood culture device, has been described as useful tool of prognosis in patients suffering from blood stream infection with *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella pneumonia*. The present study investigates the relationship between TTP and in-hospital mortality in patients with monomicrobial *Pseudomonas aeruginosa* blood stream infection (PA-BSI).
Methods: From 2006 until 2012 a retrospective cohort study was undertaken in 3 hospitals in the region surrounding Tübingen, Germany. Seventy-four patients with monomicrobial PA-BSI were studied. TTP and clinical parameters were determined and analyzed by receiver operating characteristic (ROC) analysis and Cox regression.
Results: The in-hospital mortality of our clinical cohort was 33.78%. In multivariate Cox regression, a TTP $\leq$ 18 h proved to be independently associated with mortality (HR 3.83, $P = 0.012$) along with SAPS II score (HR 1.04, $P = 0.006$), cardiac disease (HR 0.33, $P = 0.008$) and appropriate definitive antimicrobial treatment (HR 0.21, $P = 0.013$).

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Conclusions: TTP is an easy-to-measure laboratory tool for prognosis in patients with monomicrobial PA-BSI, providing useful information in addition to clinical parameters.

Introduction

Pseudomonas aeruginosa is an important Gram-negative pathogen encountered by clinicians worldwide. It has been reported to cause infection or colonization of various sites of the body.[1] Bacteremia with *P. aeruginosa* remains one of the most feared infections due to mortality rates of 20−39% depending on the hospital setting, the seriousness of underlying diseases and timely administration of appropriate treatment.[2−5] A number of studies have investigated risk factors for the acquisition of *P. aeruginosa* bacteremia and developed prognostic scores to identify patients at high risk of death.[3,5,6] However, such scores can be cumbersome during daily routine and have a limited prognostic precision. The search for easily implementable predictors of mortality in patients with *P. aeruginosa* blood stream infection (PA-BSI) is still needed.

The time to positivity (TTP), measured as the time span between the start of incubation and the automated alert signal from the blood culture instrument, is thought to reflect the bacteremia load[7,8] and has been described as an independent predictor of mortality in *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella pneumoniae* bacteremia[9−13] and as a predictor of drug resistance.[14,15] TTP also correlates with the source of infection in some settings.[16−18] Furthermore, TTP was used to discriminate between different genera and species of Gram-negative bacilli and Candida.[19,20] Martínez et al. showed that a TTP $\leq$ 12 h is not indicative of an involvement of non-fermenting pathogens in bacteremia with Gram-negative bacilli[18] but no study has addressed the potential prognostic value of TTP in PA-BSI.

The purpose of this study was to investigate the association between TTP and risk of death and source of infection in monomicrobial PA-BSI and to discuss the relative merit of TTP as prognostic tool.

Materials and methods

Setting and patients

Our retrospective cohort study is reported conformable to the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines.[21] It was conducted from 1st January 2006 until 31st January 2012 in a 1500-bed tertiary teaching hospital, a 500-bed district hospital and a 300-bed trauma center in the Tübingen area, Germany. The hospitals provide a broad spectrum of medical services, including various medical and surgical specialties, a maternity ward, dialysis and pediatric units. Organ transplantations, including bone marrow, are performed at the tertiary teaching hospital. The study has been approved by the local research ethics committee.

Study design and definitions

Patients were considered eligible if they had a blood stream infection (BSI) with $\geq$1 blood culture positive for *P. aeruginosa* and if they were $\geq$18 years. Patients with polymicrobial infections, those treated with appropriate *in vitro* susceptible antimicrobials before blood for culture was drawn and those who were not admitted to the hospital were excluded. Eligible patients were retrospectively identified from the laboratory information system using Hybase software (Tieto GmbH, Eschborn, Germany). Every patient was included only once at the time of the first positive blood culture (index culture).

The primary outcome was in-hospital mortality for any cause, and the variable of interest was time to positivity. Patient records were retrospectively reviewed by medically trained personnel that were blinded to TTP results. Clinical data gained included age; sex; nosocomial infection (defined as infection that occurred $\geq$ 48 h after hospital admission); site of infection (primary, secondary, intravascular catheter-related) according to the definition of the International Sepsis Forum Consensus Conference[22]; Charlson comorbidity score at admission[23]; baseline diseases; immunosuppression, such as HIV and/or neutropenia (neutrophil count $\leq$ 1000 cell/μl) and/or receipt of steroids (prednisolone $\geq$ 10 mg/daily or equivalent dose) and/or other immunosuppressive chemotherapy within the previous 2 months (anti-inflammatory monoclonal antibodies or anti-cancer drugs); previous surgery during hospitalization; laboratory parameters (leukocytes, cells $\times$ 10^3/μl and creatinin, mg/dl at the index culture day); and the presence of concomitant infections (infections by relevant pathogenic organisms other than *P. aeruginosa*). The patient's actual physiological status was assessed by calculating the simplified acute physiology score II (SAPS II) of the index culture day.[24]

Appropriate antimicrobial treatment was defined as systemic administration of at least one antimicrobial agent to which the isolate was *in vitro* susceptible. Monotherapy with aminoglycosides was not deemed appropriate despite *in vitro* susceptibility. Appropriate antimicrobial treatment was categorized in i) appropriate empirical treatment (AET) which must have been delivered within 24 h after samples for blood cultures were obtained, and ii) appropriate definitive treatment (ADT) which must have been delivered at any time after the index culture.

Microbiological methods and time to positivity

From all patients an approximate volume of 10 ml blood was inoculated into each aerobic and anaerobic BACTEC PLUS bottle and was promptly transported to the microbiological laboratory. Bottles with antibiotics were not used. We generally recommend the concomitant drawing of blood from at least three different peripheral punctures after disinfection. However, in practice we usually received two blood culture sets.